

PYTEST - urea, c-14 capsule

Avent, Inc.

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DESCRIPTION

PYtest¹ (¹⁴C-Urea Breath Test) is a qualitative and non-invasive method for the diagnosis of *Helicobacter pylori* (*H.pylori*). To detect *H.pylori*, ¹⁴C-urea supplied in a capsule is swallowed by the patient. If gastric urease from *H.pylori* is present, Urea is split to form CO₂ and NH₃. Ten minutes after the patient ingests the capsule, a breath sample is collected into a balloon. The breath sample is later transferred to collection fluid to trap the labeled CO₂. The liquid sample is then analyzed in a liquid scintillation counter.

The PYtest¹ Kit (¹⁴C-Urea Breath Test) is designed for use with the PYtest¹ capsule, a gelatin capsule for oral administration containing 1 μCi of ¹⁴C labeled urea. The urea is adsorbed on sugar spheres and colored yellow with fluorescein.

¹Registered Trademark or Trademark of Kimberly-Clark Worldwide, Inc.

Data on ¹⁴C-urea

Structural Formula (¹⁴C-urea): NH₂ ¹⁴C NH₂

Radiation emission: beta-emission, 49 keV_{mean}, 156 keV_{max}, no other emissions

External emission: No external radiation hazard. Low-energy beta emissions only. Maximum range of 0.3 mm in water.

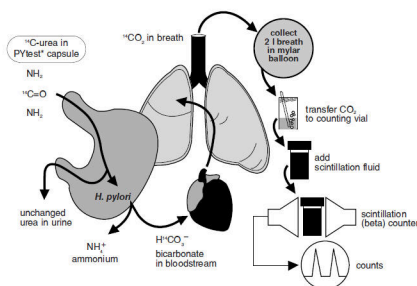
Radiological Half-life: 5730 years

Maximum effective dose equivalent (EDE) : 0.3 mrem/μCi

CLINICAL PHARMACOLOGY

The urease enzyme is not present in mammalian cells, so the presence of urease in the stomach is evidence that bacteria are present. The presence of urease is not specific for *H.pylori*, but other bacteria are not usually found in the stomach. The principle of the breath test is shown in Figure 1.

Figure 1: Principle of Breath Test



To detect *H.pylori*, urea labeled with ¹⁴C is swallowed by the patient. If gastric urease from *H.pylori* is present, urea is split to form CO₂ and NH₃ at the interface between the gastric epithelium and lumen and ¹⁴CO₂ is absorbed into the blood and exhaled in the breath.

Following ingestion of the capsule by a patient with *H.pylori*, ¹⁴CO₂ excretion in the breath peaks between 10 and 15 minutes and declines thereafter with a biological half-life of about 15 minutes. ¹⁴C-urea that is not hydrolyzed by *H.pylori* is excreted in the urine with a half-life of approximately 12 hours. About 10% of the ¹⁴C remains in the body at 72 hours and is gradually excreted with a biological half-life of 40 days.

CLINICAL STUDIES

Two studies were performed. In both studies, patients with gastrointestinal symptoms underwent the breath test and an endoscopy. During the endoscopy, biopsy samples were taken from the antral gastric mucosa for histological analysis (2 samples, Giemsa stain) and rapid urease test (1 sample, CLOtest¹). Breath samples were mailed to the TRI-MED lab where they were read in a liquid scintillation counter.

Results were reported as disintegrations per minute (DPM). Analysis for accuracy used the ten minute breath sample. A breath sample DPM <50 was defined as a negative result. DPM ≥200 was defined as a positive result. DPM in the range of 50 -199 was classified as indeterminate.

STUDY 1

Of 186 patients who had histopathology and CLOtest¹ (80 men, 106 women), 53 were infected with *H.pylori* as determined by agreement between histology and CLOtest¹. The study results are summarized below:

Table 1: Study #1 (n=186, Indeterminate results included)

Histology and CLOtest ¹					
<i>H.pylori</i>		Positive	Negative	Total	
PYtest ¹ (DPM 10m.)	Positive	51	8	59	ppv. 86%
	Indeterminate	1	8	9	
	Negative	1	117	118	npv. 99%
	Total	53	133	186	
		sensitivity 96%	specificity 88%		

Notes: PYtest¹ at 10 min. was compared to the gold standard of biopsy results in which histology and CLOtest¹ concurred. Patients who did not have both biopsy tests performed, or in whom the tests differed, were excluded from analysis. There was no statistical difference in test accuracy based on gender of patient.

ppv = positive predictive value (true positive divided by total

PYtest¹ positive)

npv = negative predictive value (true negative divided by total

PYtest¹ negative)

STUDY 2

Breath tests were performed on 436 outpatients attending gastroenterology practices at sites in the United States. Seventy-six patients (40 men, 36 women) who had histology and CLOtest¹ were evaluated. The results are summarized below:

Table 2: Study #2 (n=76, Indeterminate results included)

Histology and CLOtest ¹					
<i>H.pylori</i>		Positive	Negative	Total	
PYtest ¹ (DPM 10m.)	Positive	22	0	22	ppv. 100%
	Indeterminate	4	2	6	
	Negative	1	47	48	npv. 98%
	Total	27	49	76	
		sensitivity 82%	specificity 96%		

Notes: PYtest¹ at 10 min. was compared to the gold standard of biopsy results in which histology and CLOtest concurred. Patients who did not have both biopsy tests performed, or in whom the tests differed, were excluded from analysis. There was no statistical difference in test accuracy based on gender of patient.

ppv = positive predictive value (true positive divided by total

PYtest¹ positive)

npv = negative predictive value (true negative divided by total

PYtest¹ negative)

INDICATIONS AND USAGE

PYtest¹ (¹⁴C-Urea Breath Test) is indicated for use in the detection of gastric urease as an aid in the diagnosis of *H.pylori* infection in the human stomach. The test utilizes a liquid scintillation counter for the measurement of ¹⁴CO₂ in breath samples.

CONTRAINDICATIONS

None

WARNINGS

None

PRECAUTIONS

General

After the patient ingests the ^{14}C -urea capsule, the sample collected for test purposes is for in vitro diagnostic use only. A false positive test could occur in patients who have achlorhydria. Very rarely, a false positive test may occur due to urease associated with *Helicobacters* other than *H.pylori* (i.e. *Helicobacter heilmanni*).

Limitations of the Test

- The test has been evaluated in outpatients before elective endoscopy.
- Test results should be evaluated with clinical signs and patient history when diagnosing *H.pylori* infection.
- The performance characteristics of the test have not been established for monitoring the efficacy of antimicrobial therapies for the treatment of *H.pylori* infection.
- A negative result does not completely rule out the possibility of *H.pylori* infection. If clinical signs and patient history suggest *H.pylori* infection, repeat the PYtest¹ or use an alternative diagnostic method.
- The integrity of samples in balloons sent by air transport has not been adequately determined. In studies simulating the effects of air transport for two to seven days at temperatures of -40°C, 20°C and 55°C, no balloon failures were observed. However, the data could not provide statistical determination that no changes in $^{14}\text{CO}_2$ concentration took place.
- For ground transport, integrity of samples in balloons has not been determined beyond 7 days. During this time frame, concentration of labeled CO_2 can decrease as much as 0.36% per day.

Radioactivity

Persons concerned about very low doses of radioactivity may postpone the test or may decide to use an alternative means of diagnosis. The test produces radiation exposure equal to 24 hours of normal background. In animal experiments, such low doses of radiation do not carry measurable risk.

Preclinical studies were not conducted on ^{14}C -urea. The estimated dose equivalent received from a single administration of PYtest¹ (1 μCi ^{14}C) is about 0.3 mrem.

Information for Patients

It is necessary for the patient to fast for 6 hours before the test. The patient should also be off antibiotics and bismuth for 1 month, and proton pump inhibitors and sucralfate for 2 weeks prior to the test. Instruct the patient not to handle the capsule directly as this may interfere with the test result. The capsule should be swallowed intact. Do not chew the capsule.

Carcinogenesis, mutagenesis, impairment of fertility

No studies have been conducted with ^{14}C -urea to evaluate its potential for carcinogenicity, impairment of fertility, or mutagenicity.

Drug Interactions

Antibiotics, proton pump inhibitors, sucralfate, and bismuth preparations are known to suppress *H.pylori*. Ingestion of antibiotics or bismuth within 4 weeks and proton pump inhibitors or sucralfate within 2 weeks prior to performing the test may give false negative results.

Pregnancy

Pregnancy category C

Animal reproduction studies have not been conducted with PYtest¹ (^{14}C -urea). It is also not known whether PYtest¹ can cause fetal harm when administered to a pregnant woman or can affect reproduction capacity. PYtest¹ should be given to a pregnant woman only if clearly needed.

Nursing mothers

It is not known whether this drug is excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised when PYtest¹ is administered to a nursing woman.

Pediatric Use

Clinical studies in children have not been conducted. However, PYtest¹ is expected to work the same in children as in adults. While the dose (1 capsule) does not need to be adjusted, the child must be able to swallow the intact capsule and blow into a straw.

ADVERSE REACTIONS

No adverse reactions were reported in clinical trials.

OVERDOSAGE

Risk from radiation is negligible even with a 1000 capsule overdose (0.3 rem). If overdose occurs, the patient may drink one glass of water (150 mL) every hour to hasten excretion of the isotope. Maximum excretion of Urea is achieved at a urine output of ≥ 2.0 mL/min.

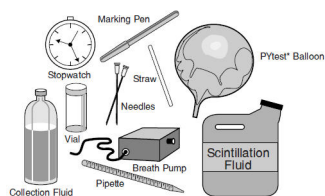
DOSAGE AND ADMINISTRATION

Materials provided

As shown in Figure 2, the PYtest¹ Kit contains:

- PYtest¹ capsule
- Two 30 mL disposable cups
- One drinking straw
- One mylar collection balloon
- One report form
- One mailing box with labels²

Figure 2: PYtest¹ Kit



2The kit includes analysis by Kimberly-Clark of one balloon from one patient at one time point.

Materials Needed but not Provided

1. Stopwatch/Timer capable of timing an interval up to 10 minutes.
2. Water (40mL)

Dosage

One PYtest¹ capsule.

Procedural Notes

- Inform the patient to fast for 6 hours prior to the test.
- The patient should be off antibiotics and bismuth for 1 month, and proton pump inhibitors and sucralfate for 2 weeks prior to the test.
- Have patient sitting at rest while doing the test.
- The capsule should not be handled directly as this may interfere with the test result.
- To avoid contamination by bacteria in the mouth, the capsule should be swallowed intact. Do not chew capsule.

Step by Step Procedure for Balloon

Table 3: Breath Sample Collection by Balloon

Before the test	1. Label balloon and fill in breath test report form.
	2. Check that all materials are present.

Minus 1	<ol style="list-style-type: none"> 1. Open the package containing the ^{14}C-urea capsule minute and tip the capsule into the empty 30 mL cup. Do not handle the capsule directly. 2. Hand the cup to the patient. 3. Fill the second cup with 20 mL lukewarm water.
0 minute	<ol style="list-style-type: none"> 1. Ask the patient to tip the capsule directly into his/her mouth, then swallow it with the 20 mL of lukewarm water. 2. Start the stopwatch when the patient swallows the capsule. 3. Discard waste (e.g., capsule packaging, used straws) according to your facility's regulations.
3 minutes	Ask the patient to drink another 20 mL of lukewarm water (in case the capsule may have lodged in the esophagus and not yet reached the gastric mucosa).
10 minutes	<ol style="list-style-type: none"> 1. Push a drinking straw into the neck of the balloon. 2. Ask the patient to hold his/her breath for 5-10 seconds, then blow up a balloon with a slow breath through the straw, filling the balloon completely. 3. Tie the neck of the balloon into a tight knot. 4. Check that the balloon label and the breath test report form are completed correctly.
After the test	Place the filled balloon and breath test report in the box and forward to Kimberly-Clark for analysis.

Quality Control

A minimum of 1 mM of CO_2 is required to perform analysis of a breath sample. The amount of breath required to provide 1 mM of CO_2 varies depending on the amount of CO_2 the patient is producing. Since a full balloon typically contains at least 1 mM of CO_2 , the balloon should be completely filled.

Results

Interpretation of results (10 minute sample)

<50 DPM	Negative for <i>H.pylori</i>
50-199 DPM	Indeterminate for <i>H.pylori</i>
≥200 DPM	Positive for <i>H.pylori</i>

The indeterminate result should be evaluated by repeating the PYtest¹ or using an alternative diagnostic method. If repeat breath testing is undertaken, careful history to exclude confounding factors should be obtained. If confounding factors are present, wait an appropriate time (refer to Table 4) before repeating the PYtest¹.

The cutoff point of 50 DPM was determined to be the mean + 3SD of results obtained in patients who did not have *H.pylori*.

DPM = Disintegrations per minute

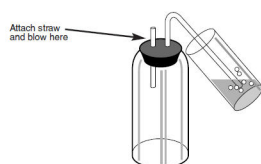
Table 4: Factors which might cause sub-optimal breath test results

Factor	Result	Comment
Recent antibiotic or bismuth (Pepto-Bismol, etc.)	false neg.	Relapse of partially treated <i>Hp</i> may take 1-4 weeks.
Omeprazole (or other proton pump inhibitors)	false neg.	These agents suppress <i>Hp</i> in 40% of patients. Discontinue for at least 2 weeks before performing the PYtest ¹ .
Resective gastric surgery	false neg.	Isotope may empty rapidly from the stomach.
Resective gastric surgery	false pos.	Patient may be achlorhydric and have bacterial overgrowth (non- <i>Hp</i> urease).
Food in stomach (also bezoar, gastroparesis)	unknown	Isotope may not come into contact with gastric mucosa. Patient may be achlorhydric and/or have bacterial overgrowth (non- <i>Hp</i> urease).

Expected Values

As shown in Figure 3 approximately 30% of patients tested will be positive for *H.pylori*.

Figure 3: Histogram showing DPM distribution for the PYtest¹.



Note: DPM groupings were calculated on a logarithmic scale. Empty DPM groupings were not included. Chart includes all patients from Studies 1 and 2.

Frequency of DPM group includes samples with DPM < Group Name.

DPM = Disintegrations per minute

Gold Standard = Agreement between histology and CLOtest¹

If the capsule is damaged or appears abnormal in any way, it may give inaccurate results.

HOW SUPPLIED

PYtest¹ Kit (¹⁴C-Urea Breath Test) is supplied as a kit containing a PYtest¹ Capsule, a clear gelatin capsule containing 1μCi of ¹⁴C-urea and breath collection equipment.

PYtest¹ Capsules are also supplied separately in unit dose packages of 1,10 and 100.

The PYtest¹ Capsule has a shelf life of two years. The expiration date is printed on the capsule label.

PYtest¹ Capsules and Kit should be stored at 15°-30°C (59°-86°F) in an area designated by each individual institution's regulations.

Rx Only

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PRINCIPAL DISPLAY PANEL - PYTEST* KIT LABEL

Kimberly-Clark* PYtest* Kit

¹⁴C-Urea Breath Test

for the detection of *Helicobacter pylori*

Contents - 10 PYtest* Capsules

PYtest* Breath Collection Accessories

For Dosage Information, Please See Package Insert

1 PYtest* capsule contains 1 μCi ¹⁴C-Urea

¹⁴C-Urea (5730years1/2, 156keV_[max] β-emission)
For In Vitro Diagnostic Use
Rx only
Store at 15°- 30°C (59°- 86°F)
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